う方向性が必要であろう．

5 内科・外科治療とのさらなる協調の時代へ

前述のように放射線治療技術の進歩により病巣への線量集中性は著しく改善している．しかし，肝胆膵領域の癌治療においては線量集中性の改善による局所効果の改善と副作用低減だけでは予後向上には限界があるのは自明である．肝細胞癌における陽子線治療，炭素イオン線治療の局所制御率90％前後と極めて高いが，生存率の向上には，術後再発予防と同様に肝内再発をいかに予防するかという点でのアプローチが今後必要と考えられる．切除後の再発予防治療として分子標的治療薬，非環式レチノイド，インターフェロン，免疫療法(癌ワクチン療法，免疫細胞療法)，B型肝炎についてはラミブジンなどの有用性が示唆されているが，放射線治療後の再発予防治療としては効果と安全性の両面でどのような治療法が最も適しているかという意味でも今後検討が必要であろう．また，胆道癌，膵臓癌の根治治療においては潜在的な転移巣制御の観点から抗癌剤との併用は必須であり現在，ジェムザールやTS-1などとの併用療法が行われている．まずは，高精度放射線治療や粒子線治療とこれら抗癌剤の併用療法に関するエビデンスの蓄積が必要であるが，将来的には有効性が期待されているエルロチニブなどの分子標的薬剤や免疫療法との併用療法の可能性についても検討されるべきだろう．

腹部・骨盤部領域の腫瘍に高線量を投与する際に最も障害になるもののひとつは腸管である．現在，粒子線(特に炭素イオン線)領域では，腫瘍と腸管が非常に近接している場合に，外科と連携し腫瘍と腸管の間に距離を保つためのスペーサー留置を行ったうえで照射治療を行うことがあり，より生体親和性の高いスペーサー材料の研究開発も進んでいる．術前・術後照射，再発時の救済治療(救済手術，救済放射線治療)とは別の外科・放射線科との連携オプションとして将来的な発展が望まれる[13]．

6 放射線生物学をベースとした治療の個別化の時代へ

線量集中性の向上により従来に比べて格段に副作用は軽くなってきているのは事実であるが，重篤な有害反応の出現は皆無でない．もちろん，線量分布や投与線量の問題が原因で起こる有害反応もあるが，想定外の重篤な副作用の多くは患者側の因子(体質)に起因している場合が多い．近年のゲノムサイエンスの進歩により遺伝子多型解析が進んでおり，遺伝子多型が薬剤への応答性，放射線への応答性に深く関与していることが判ってきている．今後，正常組織の放射線感受性に関わる遺伝子多型が網羅的に解析されることにより，有害反応が起きやすい症例，起きにくい症例が治療前に推定できるようになり，放射線治療に適した症例の選択法，リスクに応じた放射線治療の個別化が確立されることが望まれる[14]．また，放射線治療後の晩期有害事象の治療法としての再生医療の応用についても本格的な基礎研究，臨床研究が勢力的に行われていくことも期待したい．

7 最後に

未来の放射線治療の方向性について概説した．多分に個人的な意見が含まれており，内容によっては意見の異なる読者の方もおられるであろう．放射線治療に限らず癌医療を取り巻く環境は大きく変化し非常に多様化している．しかし，求められている癌治療は，「よ

り効果的で，より体にやさしい治療」であることは間違いなく，その点で，高精度放射線治療や粒子線治療への期待は非常に大きいと思われる．分子イメージング，生物学の進歩を取り入れながら，また，内科，外科との協力のもとさらに発展することが望まれる．

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食道癌

権丈雅浩*

■ はじめに

食道は頸部から腹部までの広範囲にわたる長大な管腔臓器である。食道癌の原発巣は長軸方向に広く進展し，しばしば食道内の複数箇所に病巣が認められる。浸潤の程度すなわち深達度はT病期に反映されており治療方針と予後に関わる重要な因子である。さらに原発巣の深達度に加えてリンパ節転移の部位と個数も予後因子となる。原発巣が存在する食道の部位に応じて転移が生じるリンパ節の場所とリスクは大きく異なるが，放射線治療が必要な食道癌と診断された時点でリンパ節転移を生じるリスクは決して小さくはないことがわかっている[1]。可視的なリンパ節を認めない場合でも食道癌の手術に際しては原発巣を含む食道の切除に加えて2群や3群までのリンパ節領域まで郭清する術式が標準であり，食道抜去のみの手術は根治性が低いとされている[2]。一方で放射線治療の場合にはどのリンパ節領域まで標的体積に含めるかすなわち放射線治療の対象とするかについての十分なコンセンサスがない。過去の臨床試験をみてもリンパ節領域に対する標的体積の設定は様々である。臨床現場では症例ごとにコンツーリングを行う範囲を決めることとなるが，あらかじめ各医療機関においてコンセンサスを設けておくことが望ましい。

本稿では食道癌の治療計画について，総論として準備について記した後で，標的体積の設定を原発巣，転移リンパ節，潜在的リンパ節領域にわけて解説する。コンセンサスがない事項については考え方を記すこととする。さらに計画表的体積の設定と治療に際して配慮を要するリスク臓器とその線量制約についても触れるが，病変に対する線量処方については述べないこととする。本稿で用いる標的体積の定義を表1と図1に記す。

表1　標的体積の定義

略号	定義
GTVprimary	原発巣（同じレベルの食道を含む）
GTVnode	転移陽性としたリンパ節
CTVprimary	GTVpに対応するCTV
CTVnode	GTVnに対応するCTV
CTVsubclinical	潜在的（予防的）リンパ節領域
CTV	CTVp，CTVn，CTVsをまとめたもの

* M. Kenjo　広島大学大学院　医歯薬保健学研究院　放射線腫瘍学講座
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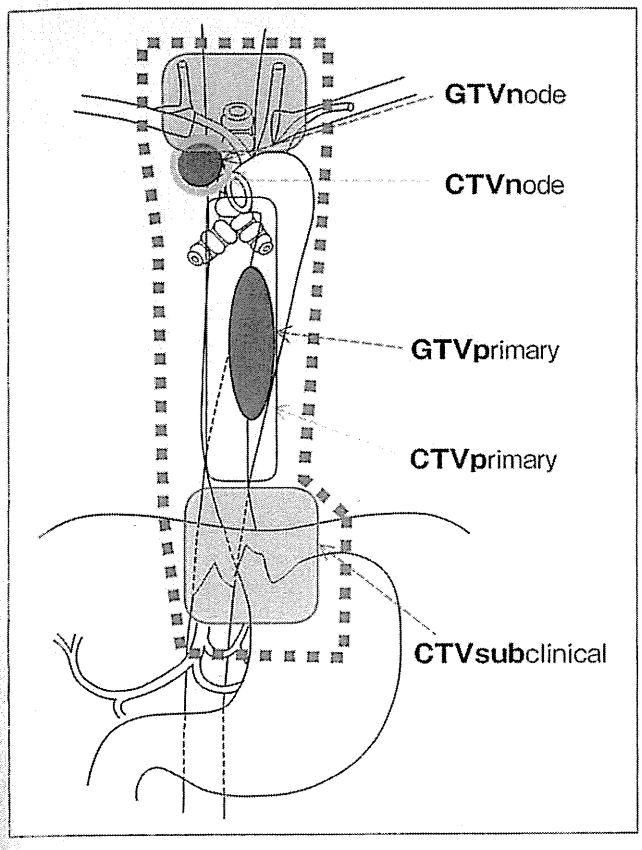

図 1　標的体積定義の概略

① 治療計画準備

CT 画像では食道癌の原発巣の部位と進展範囲の把握は困難なことがしばしばある。特に治療計画に用いられる水平断で腫瘍の上下端を正確に同定することは難しい。またリンパ節を転移陽性とするか否かも判断が難しい。放射線治療の計画に際しては実際にコンツーリングに用いる CT 画像のみではなく，内視鏡，食道造影，FDG-PET 等から得られた情報を総合して取り組むことが求められる。

食道癌の評価において内視鏡は必須の検査である。原発巣が壁内にとどまり CT 画像では存在部位が同定できない表在癌（T1a および T1b）と一部の T2 の症例では治療計画に先立って内視鏡検査を行って病巣の辺縁部にマーキング（クリッピング）を行っておく必要がある。クリップは時間がたつと脱落する可能性があるため放射線治療の計画の直前に内視鏡検査を行うようにする。内視鏡で確認できる病巣部の上下端に止血クリップなど X 線吸収のある素材でできたマーカーを脱落しないように留置する。噴門部や頸部食道など両端へのマーカー留置が困難な場合には上端もしくは下端の一方に留置し，そこからの腫瘍の長径を記録して参照する。食道癌はしばしば同時多発するため，主病巣の他にも表在性の病巣がないか内視鏡で慎重に確認する。

リンパ節転移の評価に際しては FDG-PET の併用が有用である。PET 検査結果には偽陽性，偽陰性があることを踏まえた上で個々のリンパ節を転移陽性とするか否かを慎重に判断しながら治療計画を行う。根治を目的として放射線治療を行う際は病期診断の際に転移ありと判断したリンパ節は標的体積に含めることが基本である。また PET 画像は進行例で原発巣の浸潤範囲を同定する際にも役に立つ。

瘻孔形成が疑われる深い潰瘍を伴う病巣や内視鏡が通過しない程に狭窄を来した病巣の評価には食道造影が有用である。食道透視によって潰瘍の深さを知ることは穿孔のリスク評価にも役に立つ。食道造影に用いる硫酸バリウムは CT ではアーチファクトが生じるため，治療計画の妨げとならないように食道造影の実施時期を調整する。治療計画用 CT の撮像に続いて食道造影を同日に行っておくのも一案である。

照射範囲に含まれる正常臓器，特に肺と心臓の体積を減らすためには CTV から PTV を作成する時のマージンを小さくすることが重要である。頸部食道の病変の場合には下咽頭癌など頭頸部癌と同様にシェルによる固定が役に立つ。肩まで覆うシェルを用いるか肩下げでの上肢固定が望ましい。胸部下部から腹部にかけての病巣では呼吸に伴う移動が無視できない。放射線治療の準備の際にその移動量を評価して 1cm を大きく超える場合にはそれを減じるための対策を検討した方がよい。呼吸移動対策を行って internal margin を減らすと心臓の照射体積を小さくすることができ，晩期の有害事象の低減につながる可能性がある。なお，食道癌の放射線治療では一定の条件を満たして息止めや呼吸同期など呼吸移動への対策を施した場合，診療報酬上で加算の算定が可能である。

原発巣が噴門部に及ぶ場合や胃周囲のリンパ節まで転移を認める場合など上腹部が標的に含まれる場合には放射線治療に際して食事の影響が避けられない。照射体積を小さくするために胃病変の治療に準じて治療前の飲食制限を行うことが望ましい。

表2　GTVp：原発巣のGTV　横断面方向

T stage	GTVp
T1a, T1b	病巣部を食道外壁まで全周性に囲む（厳密にはGTV+CTVの一部）
T2	
T3	食道周囲への可視的進展領域を含む CT：軟部組織濃度上昇域 FDG-PET：SUV高値域
T4	

表3　CTVp：原発巣のCTV　横断面方向

T stage	CTVp
T1a, T1b	食道外壁まで（GTVpと同じ）
T2	食道周囲への進展可能領域を含むGTVpから0.5～1cm程の範囲 解剖学的障壁を考慮 （骨・血管・肺は浸潤がなければ除く）
T3	
T4	

❷ 肉眼的腫瘍体積（GTV）および臨床標的体積（CTV）

1）原発巣

原発巣のコンツーリングでは，各水平断面で腫瘍を含む食道外壁を全周に囲んでGTVp（原発巣に対するGTV）とする。主病巣の深達度が筋層までにとどまるT2以下の場合は食道壁の外縁までをGTVpとする（病変が全周性でない場合，厳密にはここで示すGTVpはCTVpの一部を含んだものとなる）。T3-T4病変ではCTおよびPET/CTなどを参照して食道壁外への進展を含めてGTVpの輪郭を書く。表2にGTVpの設定の要点を記す。

GTVpの食道長軸方向のコンツーリング，すなわち何枚のスライスに渡ってGTVpを設定するかは食道癌の治療計画で最も大切な点である。内視鏡で腫瘍の全域が観察できた場合にはGTVpの長軸サイズは報告書に記されている腫瘍長径サイズに一致する。表在癌などCTでの病変の同定が難しい病巣は内視鏡で留置したマーカーを参照してGTVpを設定する。複数の病巣が存在する場合，内視鏡レポートでは主病巣以外については簡単な記載で済まされていることもあるので注意しておく。

内視鏡や食道造影，CTなど様々な画像診断のレポートに記載されている原発巣のサイズと設定したGTVpのサイズに乖離がないかをコンツーリング後に確認しておくことは重要である。例えば内視鏡レポートで「門歯から28cmから34cmに渡って……」と記載される病変の場合にはGTVpの長径は少なくとも6cmになるはずである。水平断画像を用いてGTVpのコンツーリングを行った後にその範囲が妥当かを矢状断と冠状断画像で見直し，食道造影やPET画像と対比させて確認することも大切である。

次いで原発巣から周囲への微視的な進展を考慮してCTVpを設定する（表3）。粘膜下層までにとどまる表在癌（T1b以下）ではそれぞれの水平断面でのGTVpとCTVpは同一としてよい。一方，筋層以深に浸潤する病巣（T2以上）ではGTVp周囲の軟部組織に1cm程度のマージンを設定してCTVpのコンツーリングを行う。この時，GTVpに自動的に一律のマージンを加えてCTVpとするのではなく，解剖学的な障壁を考慮して病変が進展しうる方向に対して加筆と修正を行う。通常は椎体の骨梁部分や心臓と大血管の内部，気管，気管支内部の空気はCTVpに含めない。一方で，大動脈や気管支の壁に沿って回り込むように腫瘍が進展しうることを念頭に置いておく。図2に水平断方向のコンツーリングの例を示す。

食道癌は粘膜面，粘膜下を食道の長軸方向に広く進展することが知られている。手術例の病理標本を検討した報告で原発巣の壁内での微視的進展は多くは可視的な辺縁から3cmまでの範囲と記されている[3]。これに従ってGTVpに対して食道長軸方向に2～4cm程度のマージンを加えてCTVpとすることが一般的である。この時もGTVpとして設定した範囲を自動的に頭尾側方向に2cm拡張するのではなく，解剖学的に妥当と考えられる方向に向けて拡大してCTVpを設定する必要がある。表在癌の場合は食道外壁のコンツーリングを行うスライスを2～4cm分増やすようにする。

原発巣が離れて複数カ所に認められる場合，いわゆるスキップ病変がある場合にはその間の部分の食道をすべて含めて連続した一つのCTVpとすることも考慮する。内視鏡で認めるルゴール不染領域や狭

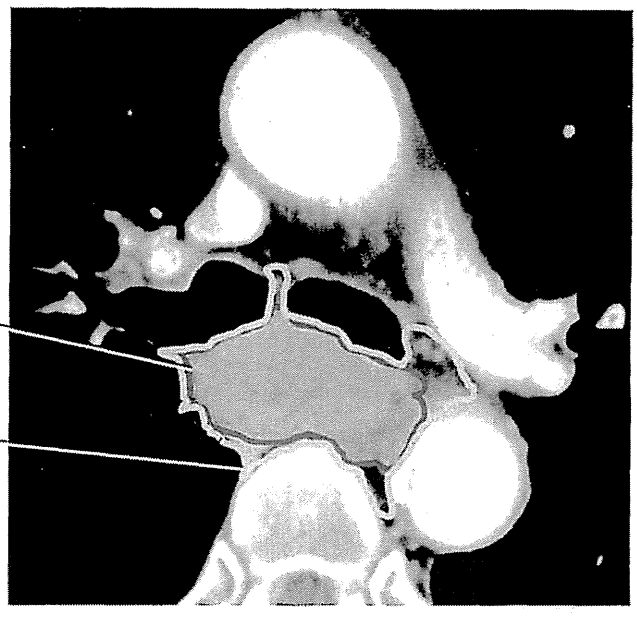

図2　T3病変に対する解剖学的障壁を考慮した臨床的標的体積の設定（CTVp）

帯域光観察（Narrow Band Imaging）での形態変化領域などのいわゆる前がん病変をCTVpとするか否かについてはコンセンサスがない。表在性病変の存在が疑わしい部位のすべてを生検して確認することも実際には困難である。これから行う放射線治療によって原発巣が制御できる可能性が高いことが予想され，広いCTVpを設定した際の照射体積の増加が容認できる程度にとどまるのであれば，これらの領域もCTVpに加えておき，主病巣と同時に治療を行うことは妥当と思われる。近接する部位に新たな病巣が出現した場合に追加で放射線治療を行うことが難しい場合もあるためである。一方でこれらの領域をCTVpに含めないでおく場合には治療後に密な経過観察を行い，もし新たな病巣が出現した場合には時期を逸することなく，内視鏡的切除などが行えるように備えておく。

2）転移リンパ節

画像診断で転移陽性と判断したリンパ節の輪郭をとってGTVn（リンパ節に対するGTV）とする。CT診断ではリンパ節のサイズをもとに短径が1cmもしくは5mmを超える場合に陽性とされることが多い。しかし，これよりもサイズが小さくともFDG-PETで強い集積を認めるリンパ節や球形で辺縁が良く造影され内部は低吸収域となるリンパ節は転移があるものとみなしておくことが妥当である。

リンパ節への転移は通常は被膜内にとどまっているものとしてCTVマージンを設定せずに，GTVn＝CTVnとする。しかし，食道癌ではしばしば腫大したリンパ節が被膜外に進展し，その周囲への浸潤が臨床的に問題となる。腫大したリンパ節の変形が強い場合や辺縁が不整の場合には節外への浸潤があるものと考えて対応することが妥当である。嗄声がある症例で反回神経リンパ節の腫大を伴う場合には，リンパ節による神経の圧迫と浸潤も疑う。嚥下困難が原発巣ではなく腫大したリンパ節によって生じていることもある。このようにリンパ節転移病巣が周囲に進展している可能性がある場合は，原発巣に対するCTVpの設定に準じてGTVnの周囲に1cm程度のマージンを設定してCTVnを定義する。

3）潜在的リンパ節領域

画像診断で転移はないとするが臨床的にはリンパ節転移のリスクがある領域，すなわち微視的（micro）なリンパ節転移が生じうる領域を潜在的リンパ節領域とし，本稿ではCTVsと定義する。これらは予防領域ともいわれ，手術の際には食道切除とあわせてこの領域のリンパ節郭清が行われる。食道癌はセンチネル理論が確立されていない分野であり，最初に転移が生じるリンパ節が原発巣の近傍に位置しているとは

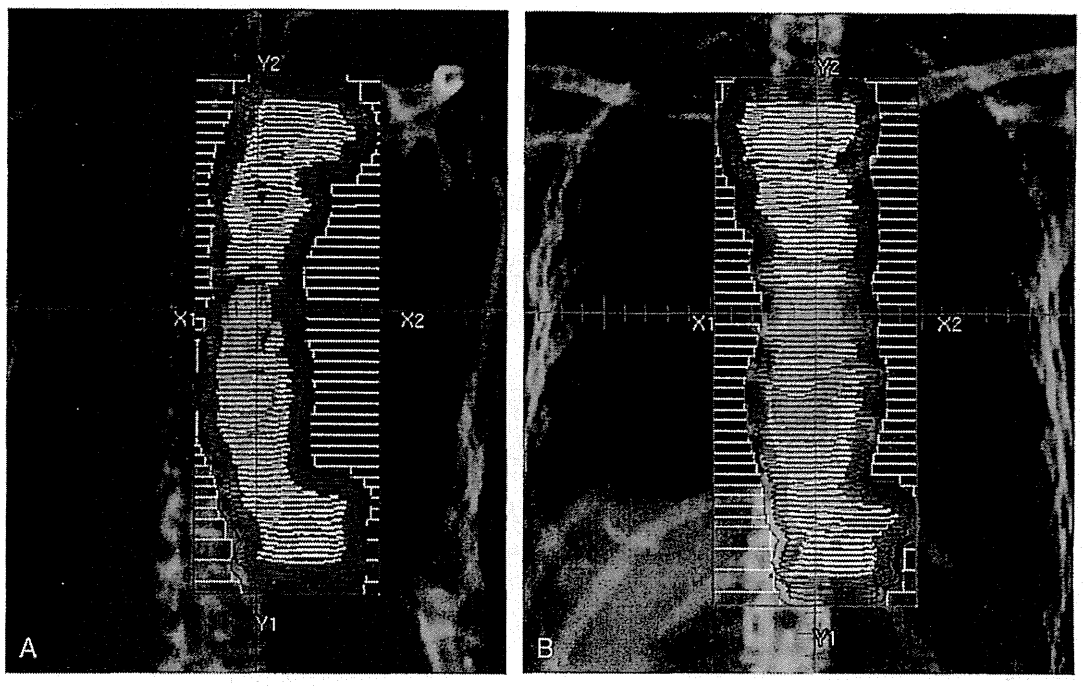

図3　CTVsを含んだ標的体積設定
A　ガントリ角度　320°の照射野　B　ガントリ角度　0°の照射野　原発巣Mt-Lt：CTVsに#101, #106rec, #1, #2を含む場合のPTV。

限らない。胸部中部食道癌のリンパ節転移は下頸部から上腹部までの広範囲に生じうる。食道癌取扱い規約では転移が生じるリスクを反映させてリンパ節の群分類が行われている。

手術例では3群もしくは2群の領域の予防郭清を行うことが予後を改善にすると本邦から報告されている[1]。食道癌取扱い規約には原発巣の部位ごとに郭清の対象となるリンパ節群が提示され，病期にも反映されている[4]。一方，放射線治療においては計画時にどのようにCTVsを設定して，治療の対象とするかに関しての十分なエビデンスとコンセンサスがない。国内外で過去に行われた臨床試験でもCTVsを設定するものとしないもの，設定する場合のその範囲に関しては様々である。

CTVsの設定に際しては食道癌取扱い規約第10版に示される図を参照し，食道原発巣の部位に対応するリンパ節領域をコンツーリングする。ガイドラインにはCTVsとする際にN1およびN2に対応する領域（いわゆる2群）までを含めることが示されている[5]。ただし取扱い規約に記載されるリンパ節領域は，「この領域にリンパ節が存在した場合XX番とする」というように画像や肉眼で同定できるリンパ節に番号を付して病期を決定するためのものであり，図で面塗りされる領域全体が一様に潜在的な転移リスクを有しているのではないことに留意する。実際に2群とされる領域の全体を一律にCTVsとして治療計画を進めると照射体積が大きくなりすぎることがあるので注意する。図3にCTVsを含んだ標的体積設定の1例を示す。

反回神経リンパ節（#106recRおよびL）は食道癌が転移を来すリスクが高いリンパ節であり，手術例では郭清が不十分な際にはしばしば再発する部位として知られている。放射線治療の際には，原発巣が頸部～胸部中部に存在するとき，少しの工夫で反回神経リンパ節の領域を照射体積に十分含めることができるため，この領域をCTVsに設定して治療の対象としておくことが妥当である。上縦隔から再発した病巣は救済手術が難しく，照射体積の辺縁部に生じると再度放射線治療を行うとしても十分な線量投与が困難となり，これが予後にも関わりうるためである。私見だが頸部気管傍リンパ節（#101）は反回神経リンパ節等の上部縦隔のリンパ節を転移陽性とする場合には含めたほうがよい。この領域をCTVsに含めることによる有害事象リスクの増加は大きくはない。転移陽性のリンパ節があってGTVnを設定した場合に，

その近傍で転移のリスクが高いことが判明している領域をCTVsとして含んでおくという考え方は理にかなっている。

一方，原発巣が胸部上部や頸部にあってGTVnとして設定するリンパ節がない場合すなわち臨床的にN0の場合には噴門部リンパ節（#1，#2）をCTVsに含めないでよいと思われる。もし噴門部リンパ節に対して予防的な放射線治療を行うとしても，心臓の有害事象発生のリスクを減じるために原発巣周囲とは切り離してこの領域に別個に照射体積を設定する方法もある。原発巣のサイズが大きく，放射線治療を行っても制御できる可能性が決して高くないと予想される場合には，そこから離れた潜在的なリンパ節領域までCTVsとしないでよいだろう。もし放射線治療後に原発巣が制御できているようであれば，後発病変についても生じた際に追加の放射線治療によって制御できる可能性がある。

食道癌のリンパ節転移は病態が多様なため臨床試験で結論を出すことが難しい分野である。時には照射体積の辺縁部にリンパ節再発を認めて痛い思いをすることがある。最終的に潜在的な領域をどこまでCTVpとして設定して放射線治療の対象とするかは担当する医師の判断に委ねられる。予防照射を行った領域ではリンパ節に再発する率は低下すると予想されるが，それが生存率の改善にどの程度貢献するかは定かではない。離れた領域に転移が出る患者は遠隔転移を生じるリスクも高く，領域のみを制御するのでは不十分という考え方もある。再発率の低下が生存に結びつく可能性と照射体積が拡大することによって新たな有害事象が発生する可能性を勘案してCTVsの設定を判断することとなる。いずれにしても医療機関での基本となる考え方を持っておき，基準を設けておくことが望ましい。

③ 内的標的体積（ITV）および計画標的体積（PTV）

上記の過程で設定したCTV（CTVp，CTVn，CTVsを総合したもの）に対してどの位のマージンを加えて内的標的体積（ITV）を設定し，最終的に計画標的体積（PTV）を作成するかは治療現場の状況によって異なる。教科書にはCTVに対するPTVマージン（Internal margin：IMとSet-up margin：SMを併せたもの）は左右と背腹方向は1cm程度，頭尾側方向は1～2cmと記されていることが多い。しかし，頸部食道と腹部食道では1回の治療時間中の動き，特に呼吸に伴うって生じる移動量は随分と異なる。GTVが大きい場合や予防領域（CTVs）を設定してCTVが大きくなった場合には，このPTVマージンの取り方によって正常臓器，特に心臓と肺の照射体積が大きく違ってくる。PTVマージンを大きく設定したために脊髄の線量制約に触れてしまい，やむを得ずPTVを一部切り込んだ照射門を設定しなければいけないこともある。治療計画の準備段階からPTVマージンを減じるための様々な工夫を行い，安全で確実な治療を目指すことが大切である。なお食道癌の治療においては中部から下部縦隔で左右方向の照射野サイズは8cmを超えないようにすることが推奨されている。

④ リスク臓器

食道はその周囲を心臓，大血管，肺など生命機能を維持するために重要な臓器によって取り囲まれている。食道癌の治療後にもこれらの臓器の機能が維持されている必要があることから，治療計画の段階でリスク臓器のコンツーリングを行い，設定した線量制約を満たすようにしておくことは重要である。

症例ごとに照射体積が異なり，関わる臓器と有害事象が発生するリスクも異なることが食道癌放射線治療の特徴である。リスク臓器として設定する臓器（OAR：Organ at Risk）としては，心臓，肺，脊髄が重要である。その他に甲状腺，腕神経叢，大動脈や鎖骨下動脈などの大血管もあげられる。腹部のリンパ節では肝臓や腎臓などが照射体積に含まれることがある。CTVpの外部となる食道と胃もリスク臓器と考えてよい。治療計画に際して各リスク臓器に対してセットアップや動きを考慮したマージンを加えてPRV（Planning Risk organ Volume）を設定し，このPRVに対して線量制約を設ける。その案を表4に示す。ただしOARからPRVをどのように設定するかすなわちOARに対するマージン設定についてはまだ十分なコンセンサスがない。マージンを設定せずにそのままOAR＝PRVとして取り扱うことがある一方

表4　食道癌の治療計画におけるリスク臓器設定と線量制約の例

臓器	PRV（Planning Organ at Risk Volume）	線量制約
心臓 (SERIAL)	心臓全体（OAR → PRV 未確定）	照射体積を最小に D_{mean} < 50 Gy
肺 (PARALLEL)	肺全体	V20 Gy < 30% V10 Gy < 45%
脊髄 (SERIAL)	脊柱管＋2～5mm	D_{max} < 50 Gy D_{1cc} < 45 Gy
甲状腺 (PARALLEL)	甲状腺全体	食道癌治療では 設定しない

で，周囲 5mm とすることもある。脊髄については脊柱管もしくは脊柱管+数 mm とすることがある。

肺では肺癌治療に準じて V20 Gy（全肺のうち 20 Gy が照射される体積の割合）が線量制約の基準となる。近年は V10 Gy や V5 Gy などのより小線量が照射される体積の重要性を指摘する報告もある。喘息など慢性呼吸器疾患を持つ症例ではより厳しい線量制約を適用することが望ましい。心臓については照射体積と線量の両方が有害事象発生に関与することが示されている。心筋梗塞や難治性の心嚢水貯留を避けるためには可能な限り線量と体積を低減する。甲状腺や CTVp の外となる食道には一般に線量制約を設定しない。しかし甲状腺に高線量が照射された場合には甲状腺機能低下症を生じるリスクがある。腹部食道から胃に対しては難治性潰瘍のリスクを考慮して最大線量を 50 Gy から 56 Gy 程度までとしている施設もある。振り返って有害事象の評価を行うことを念頭においてリスク臓器のコンツーリングを行い，線量体積ヒストグラム（DVH）を作成しておくことが求められる。

■ ま と め

食道癌の治療計画では病変の存在，進展部位に応じて症例ごとに特化した照射体積の設定が必要であり，あらかじめ十分な情報を入手しておくことが求められる。放射線治療計画に際しては病期診断を踏まえつつ，浸潤と転移の可能性を臨床的に妥当か否かの立場から再検討して標的体積を設定することが求められる。丁寧なコンツーリングに基づく適切な照射方法の設定が治癒率の改善と有害事象の低減に役立ちうることを心において治療計画に取り組んでいただければ幸いである。

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Summary

Target contouring for esophageal cancer

Tailor maid setting of target volume according to the tumor location and invasion is essential for radiotherapy planning of esophageal cancer. When contouring the gross tumor volume and clinical target volume, estimation of microscopic invasion and subclinical lymph nodes metastases and evaluation of clinical validity is needed.

Masahiro Kenjo
Department of Radiation Oncology
Hiroshima University Graduate School

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Long-term results of concurrent chemoradiotherapy using cisplatin and vinorelbine for stage III non-small-cell lung cancer

Hidehito Horinouchi,[1,6] Ikuo Sekine,[1] Minako Sumi,[2] Kazumasa Noda,[3] Koichi Goto,[4] Kiyoshi Mori[5] and Tomohide Tamura[1]

[1]Division of Internal Medicine and Thoracic Oncology, [2]Division of Radiation Oncology, National Cancer Center Hospital, Tokyo; [3]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama; [4]Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa; [5]Department of Medical Oncology, Division of Thoracic Oncology, Tochigi Cancer Center, Utsunomiya, Japan

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Concurrent chemoradiotherapy is the standard treatment for unresectable stage III non-small cell lung cancer (NSCLC). The long-term feasibility and efficacy of vinorelbine and cisplatin with concurrent thoracic radiotherapy were investigated. Eighteen patients received cisplatin (80 mg/m^2) on day 1 and vinorelbine (20 mg/m^2 in level 1, and 25 mg/m^2 in level 2) on days 1 and 8 every 4 weeks for four cycles in a phase I trial. Ninety-three patients received the same chemotherapy regimen except for the fixed vinorelbine (20 mg/m^2) dosage and consolidation therapy with docetaxel (60 mg/m^2, every 3 weeks). The thoracic radiotherapy consisted of a single dose of 2 Gy once daily to a total dose of 60 Gy. A total of 111 patients were analyzed in the present study: male/female, 91/20; median age, 60 years; stage IIIA/IIIB, 50/61; and squamous/non-squamous histology, 26/85. The 3-, 5-, and 7-year overall survival rates (95% CI) were 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.2% (15.8–31.4), respectively. The median progression-free survival and median survival time (95% CI) were 13.5 (10.1–16.7) months and 30.0 (24.3–38.8) months, respectively. Four patients (4%) experienced Grade 5 pulmonary toxicities from 4.4 to 9.4 months after the start of treatment. In conclusion, approximately 15% of patients with unresectable stage III NSCLC could be cured with chemoradiotherapy without severe late toxicities after 10 months of follow-up. Although based on the data from highly selected population participated in phase I and phase II trial, this analysis would strengthen and confirm the previous reports concerning concurrent chemoradiotherapy with third generation cytotoxic agents. (*Cancer Sci* 2013; 104: 93–97)

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for 25–30% of all lung cancer cases.[1,2] Because of the equal frequency of local and distant recurrences, the combination of systemic chemotherapy and thoracic radiotherapy has been established as a standard of care for patients with stage III NSCLC.[3] Concurrent chemoradiotherapy is superior to a sequential approach, as shown by phase III trials in stage III NSCLC.[4,5]

Ohe *et al.*[6] reported the long-term follow-up analysis of concurrent chemoradiotherapy with former generation chemotherapy agents (median survival time 16.1 months, and 7-year overall survival rate 12.0%). Few researchers, however, have reported follow-up data of longer than 5 years after concurrent chemoradiotherapy with third-generation chemotherapy. The long-term safety and efficacy of vinorelbine and cisplatin with concurrent thoracic radiotherapy were investigated.

Materials and Methods

Study selection. Two previous studies were included in this analysis. One was a phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine, and the other evaluated docetaxel consolidation therapy following concurrent chemoradiotherapy.[7,8] These studies were approved by the institutional review board at each institution. Written, informed consent was obtained from all participating patients.

Patient selection. The two studies had similar eligibility criteria. They were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and adequate organ function, including bone marrow, liver, kidney, and lung. Patients were diagnosed to have unresectable disease based on a consensus of thoracic oncologists including surgeons in each institution. The exclusion criteria were reported in previous papers.[7,8]

Treatment schedule. In the phase I study, treatment consisted of chemotherapy with four cycles of cisplatin and vinorelbine (20 mg/m^2 in level 1, and 25 mg/m^2 in level 2) and concurrent thoracic radiotherapy (see below). In the other study, treatment consisted of a chemoradiotherapy portion with three cycles of cisplatin and vinorelbine followed by a consolidation portion with three cycles of docetaxel. Cisplatin (80 mg/m^2) was administered every 4 weeks by intravenous infusion for 60 min with 2500–3000 mL of fluid for hydration. Vinorelbine 20 mg/m^2 diluted in 50 mL of normal saline was administered intravenously on days 1 and 8 every 4 weeks. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid. In the docetaxel (60 mg/m^2, every 3 weeks) consolidation trial, consolidation therapy was started sequentially in patients whose general condition was acceptable. Follow-up computed tomographies after chemoradiotherapy were scheduled as follows; every 2–4 months during the 1 year, every 6 months in the 2 and 3 years, and every 1 year thereafter.

Thoracic radiotherapy was delivered with megavoltage equipment ($\geq$6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions, including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor

[6]To whom correspondence should be addressed.
E-mail: hhorinou@ncc.go.jp

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and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. Computed tomography (CT) scan-based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking into account subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in the shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5–1.0-cm margins laterally and 1.0–2.0-cm margins craniocaudally, taking into account setup variations and internal organ motion. Lung heterogeneity corrections were not used.

Toxicity assessment. Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria version 2.0 issued in 1998, and late toxicities associated with thoracic radiotherapy were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.[9] Late toxicities were defined as those that occurred or persisted 90 days after completion of radiotherapy. The detailed methods of treatment modification due to toxicity were reported in previous papers.[7,8]

Response evaluation. In the phase I trial, the objective tumor response was evaluated according to the World Health Organization (WHO) criteria issued in 1979.[10] The Response Evaluation Criteria in Solid Tumors were used to evaluate objective tumor response in the docetaxel consolidation trial.[11] Local recurrences were defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence was defined as the development of malignant pleural and pericardial effusions; and distant recurrence was defined as the appearance of distant metastases.

Statistical analyses. Progression-free and overall survival times were estimated by the Kaplan–Meier method, and confidence intervals (CIs) were based on Greenwood's formula.[12] Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Patients who were lost to follow-up without an event were censored at the date of their last known follow-up. A CI for response rate (RR) was calculated using methods for exact binomial CIs. To investigate the association between survival and factors related to patient characteristics, the Cox regression model was used. Potential factors investigated were as follows: age (in 10-year increments), sex, body weight loss ($\leq 5.0\%$ *vs* $\geq 5.1\%$), histology (squamous cell carcinoma versus non-squamous cell carcinoma), T factor (T1/2 *vs* T3/4), N factor (N0-2 *vs* N 3), and stage (IIIA *vs* IIIB). The STATA 10 for Windows software package (StataCorp LP, College Station, TX, USA) was used for statistical analyses.

Results

Characteristics of the patients. From October 1999 to June 2003, 13 patients were registered at dose level 1 and five at dose level 2 of the phase I study, and 93 patients were enrolled in the docetaxel consolidation trial. Thus, a total of 111 patients were analyzed in the present study. The participants' characteristics were as follows (Table 1): male/female 91/20; median age (range) 60 (31–74) years; body weight loss $\leq 5.0\%/\geq 5.1\%$ 96/14; stage IIIA/IIIB 50/61; and squamous/non-squamous histology 26/85.

Table 1. Patients' characteristics

	Clinical trial		
	Phase I trial†	DTX consolidation‡	Total
Number of patients	18	93	111
Age (years)			
Median	58.5	60	60
Range	48–69	31–74	31–74
Sex			
Male	15	76	91
Female	3	17	20
Performance status			
0	4	32	36
1	14	51	65
Unknown	0	10	10
Body weight loss (minus, %)			
0	11	72	83
0.1-5.0	4	9	13
5.1–	3	11	14
Unknown	0	1	1
Clinical stage			
IIIA	9	41	50
IIIB	9	52	61
N factor			
N0	0	6	6
N1	0	3	3
N2	11	58	69
N3	7	26	33
T factor			
T1	1	18	19
T2	6	31	37
T3	7	13	20
T4	4	30	34
Unknown	0	1	1
Histology			
Adenocarcinoma	14	57	71
Squamous cell carcinoma	3	23	26
Adenosquamous	1	0	1
Large cell carcinoma	0	6	6
NOS§	0	6	6
Others	0	1	1

†The phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine. ‡The docetaxel consolidation therapy following concurrent chemoradiotherapy study. §Non-small cell lung cancer not otherwise specified.

Treatment delivery. Full cycles (four in the phase I trial, three in the docetaxel consolidation trial) of cisplatin and vinorelbine and the full dose (60 Gy) of thoracic radiotherapy were administered in 94 (85%) and 102 (92%) patients, respectively. The delay in radiotherapy was less than 5 days in 74 (67%) patients. In the docetaxel consolidation trial, 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy, mainly because of toxicities. Of 91 patients with relapses, 27 (30%) received gefitinib as salvage treatments.

Objective tumor response and survival. The objective response rate was 82.0% (95% CI, 74.5–89.1). The 3-, 5-, and 7-year progression-free and overall survival rates (95% CI) were 21.0% (13.9–29.1), 15.7% (9.5–23.4), 14.4% (8.4–22.0), and 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.1% (15.7–31.4), respectively (Fig. 1). The median progression-free survival and median survival time (95% CI) were 13.4 (9.8–16.4)

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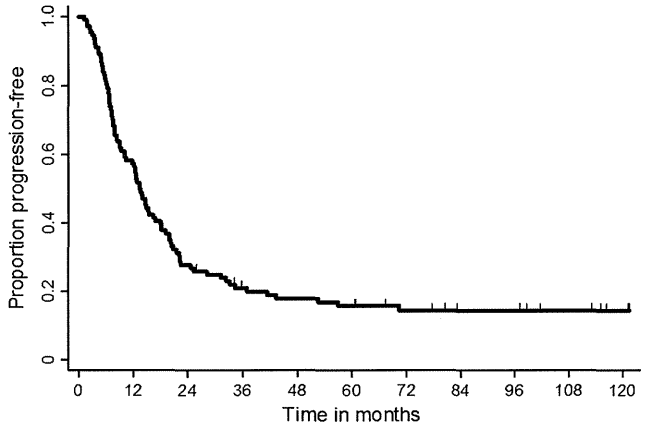

Fig. 1. Progression-free survival (n = 111). The median progression-free survival is 13.5 months (95% confidence interval [CI] 10.1–16.7).

months and 30.0 (24.5–38.8) months, respectively (Fig. 2). There was no significant difference in survival results between subgroups; patients with or without docetaxel consolidation and patients with or without gefitinib.

Pattern of relapse. Relapses were noted in 91 (82%) of 111 patients. Initial relapse sites were local alone in 39 (42%) patients, regional alone in 5 (5%), and distant alone in 38 (41%), including 17 (18%) patients with brain metastases as a sole recurrence site. Brain metastases were detected in 19 (21%) patients and were the most frequent sites of distant metastases. Brain metastases were detected within 3 years of initial treatment, and the last brain relapse was observed after 33 months of follow-up (Table 2). Three (3%) patients experienced adrenal metastases as a first relapse site.

Late toxicities. Grade 1, 2, 3, and 5 late pulmonary toxicities were observed in 18 (16%), 15 (13%), 3 (3%), and 4 (4%) patients, respectively. Seventy-two (64%) patients did not experience late pulmonary toxicities (Table 3). Four cases of grade 5 pulmonary toxicity developed at 4.4, 5.9, 9.4, and 9.6 months, respectively, after the treatment started. Late esophageal toxicities were observed in three patients (one grade 1 and two grade 3).

Causes of death in long-term survivors. There were 67 (60%) patients that survived 24 months or more from the initial treatment. Among them, five patients died because of reasons other than lung cancer. One patient was diagnosed as having pharyngeal cancer at the point of 35 months and died 4 months later. Other than malignancies, community-acquired pneumonia (one patient at 43 months), sudden death due to unknown etiology (two patients at 41 and 42 months) and suicide (one patient at 29 months) were reported, respectively.

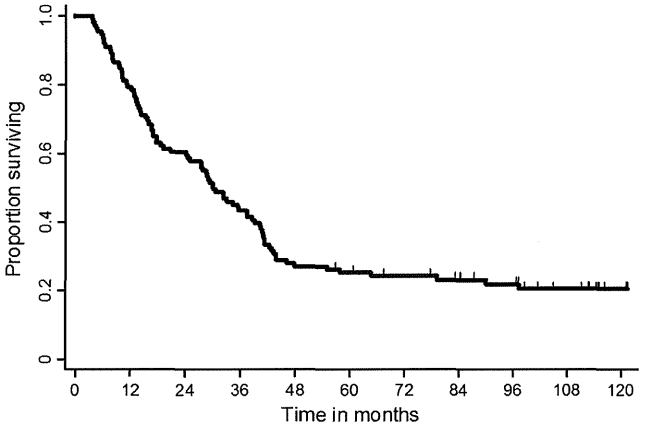

Fig. 2. Overall survival (n = 111). The median overall survival is 30.0 months (95% confidence interval [CI] 24.3–38.6).

Table 2. Sites of initial relapse

Site of recurrences	Number of relapses			
	<1 year	1–3 years	>3 years	Total (%)
Local	16	21	2	39 (42)
Distant	23	12	3	38 (41)
Distant without brain	12	4	3	19 (21)
Distant including brain	1	1	0	2 (2)
Brain only	10	7	0	17 (18)
Regional	3	2	0	5 (5)
Others (L/D/R)†	3	5	1	9 (10)
Unknown	–	–	–	2 (2)

†Others includes 2 Local+Regional relapses, 6 Local+Distant relapses, and 1 Local+Regional+Distant relapse.

Table 3. Late pulmonary toxicities§

Toxicity grades	Clinical trial		Total (%)
	Phase I trial†	DTX consolidation‡	
Without late toxicity	10	62	72 (64)
Grade 1	4	14	18 (16)
Grade 2	3	12	15 (13)
Grade 3	1	2	3 (3)
Grade 4	0	0	0
Grade 5¶	0	4	4 (4)

†The phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine. ‡The docetaxel consolidation therapy following concurrent chemoradiotherapy study. §Late toxicities were defined as those that occurred or persisted 90 days after completion of radiotherapy. ¶The Grade 5 pulmonary toxicities developed at 4.4, 5.9, 9.4, and 9.6 months after the treatment started.

Predictive factors for survival. The associations between overall survival and patients' characteristics (age [in 10-year increments], sex, body weight loss [$\leq 5.0\%$ *vs* $\geq 5.1\%$], histology [squamous cell carcinoma versus non-squamous cell carcinoma], T factor [T1/2 *vs* T3/4], N factor [N0-2 *vs* N 3], and stage [IIIA *vs* IIIB]) were also examined using Cox regression analysis. Age was significantly associated with survival (hazard ratio [HR] 1.34, 95% CI 1.02–1.75, Table 4).

Discussion

Concurrent chemoradiotherapy has been established as a standard treatment for patients with unresectable locally advanced NSCLC. The long-term feasibility and efficacy of vinorelbine and cisplatin chemotherapy with concurrent thoracic radiotherapy were investigated. The 3-, 5-, and 7-year overall survival rates (95% CI) were 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.1% (15.7–31.4), respectively. Older age was associated with poor survival on multivariate analysis (HR 1.34, 95% CI 1.02–1.75).

Two phase III trial examined the efficacy and safety of newer generation cytotoxic agents in concurrent chemoradiotherapy for patients with locally advanced NSCLC.[13,14] The 5-year survival rates (around 20%) were comparable to cur-

Table 4. Cox proportional hazard model for assessment of overall survival

Factors	Hazard ratio	95% CI	*P* value
Age			
10-year increment	1		
	1.34	1.02–1.75	0.03
Sex			
Female	1		
Male	1.23	0.69–2.31	0.46
Body Weight Loss			
<5.0%	1		
>5.1%	1.19	0.69–2.11	0.51
Histology			
Non-squamous	1		
Squamous	1.31	0.80–2.19	0.28
T factor			
T1/2	1		
T3/4	0.91	0.53–1.61	0.77
N factor			
N 0–2	1		
N 3	1.05	0.55–2.08	0.85
Stage			
IIIA	1		
IIIB	0.97	0.52–1.83	0.93

rent analysis. To date, the present report (median survival time 30 months and 7-year overall survival rate 23.1%) is one of the longest observation periods after concurrent chemoradiotherapy using third-generation agents for locally advanced NSCLC. Recently, Tokuda *et al.*[15] reported a favorable long-term survival data (median survival time 2.1 years and 5-year survival rate 31%) of concurrent thoracic radiotherapy with docetaxel and cisplatin in a phase II trial conducted by Okayama Lung Cancer Study Group (OLCSG). It seems that the result of these analyses were about twice better than that of the previous long-term report of chemoradiotherapy with former generation agents by Ohe *et al.*[6] (median survival time 16.1 months and 7-year overall survival rate 12.0%) and others.[16]

Of the 91 patients with relapses, 85 (93%) experienced recurrence within 3 years after initial treatment. Local relapses (37 patients, 41%) and distant relapses (35 patients, 38%) were equally frequent. After 3 years of follow-up, two local, three distant (without brain), and one mixed-site recurrence was observed. Considering the proportion of local recurrence was similar to the OLCSG 0007 trial, a better strategy to control local relapse is a key to improving survival in locally advanced NSCLC.[13] To gain a better local control, the radiation therapy oncology group (RTOG) conducted a phase III trial (RTOG 0617) to examine a higher dose (74 Gy) of radiotherapy with concurrent chemotherapy. However, the experimental arms of higher radiotherapy were terminated early because of survival futility.[17] We recently reported early termination of a multicenter phase II trial of high-dose thoracic radiotherapy (72 Gy) because of slow accrual and pulmonary toxicities.[18] Based on these results, development of another strategy such as surgery followed by induction therapy might offer a better local control in selected patients.[19] On the other hand, 11 of 20 brain relapses as a first recurrence were found within a year of initial treatment. Several authors reported that brain metastases were frequent early in the course after the initial treatment of stage III NSCLC.[20,21] According to our findings and previous reports, intensive brain surveys might be indicated for such patients no longer than 3 years from initial chemoradiotherapy.

The frequency and control of late toxicities, especially lung injury, have been emphasized along with the improvement of survival by concurrent chemoradiotherapy in stage III NSCLC. In the present analysis, four patients (4%) in the docetaxel consolidation trial experienced grade 5 pulmonary toxicities 4.4–9.6 months from initial treatments. On the other hand, life-threatening pulmonary toxicities were not reported in phase I trial. (Table 3) This difference in the frequency of severe pulmonary toxicities might be related to consolidation docetaxel because the dose of cisplatin (80 mg/m^2), vinorelbine (20 mg/m^2) and thoracic radiotherapy (60 Gy) were the same in these two trials except for five patients who received 25 mg/m^2 of vinorelbine in the phase I trial.[7,8] A relatively higher frequency of pulmonary complications was also reported in the experimental arm of the previous phase III trial that examined docetaxel as a consolidation therapy after concurrent chemoradiotherapy.[22,23] Although a note of caution might be indicated with docetaxel, the present result suggests that severe pulmonary toxicities were rare after 10 months from concurrent chemoradiotherapy.

According to recent trials, about half of Japanese patients with locally advanced lung cancer survive more than 2 years after concurrent chemoradiotherapy.[13,14] In those who survived more than 2 years, mortalities due to second primary malignancies and etiologies other than lung cancer were reported by several authors.[15,24] Five patients (4.5%) died without recurrence of lung cancer and whose causes of death were as follows: second primary malignancy (pharyngeal cancer, one patient), community-acquired pneumonia (one patient), sudden death due to unknown etiology (two patients) and suicide (one patient), respectively. With an even greater proportion of patients cured by modern therapies including combined modality treatments, it would be increasingly important to consider and evaluate an appropriate care and monitoring for survivors.

In the present analysis, older age was significantly associated with poor survival (HR 1.34, 95% CI 1.02–1.75) after adjusting for sex, degree of weight loss, histology, T factor, N factor, and stage. In the previous literature on concurrent chemoradiotherapy with cisplatin and vinorelbine, age ($\geq$70 years) was marginally associated with poor survival (HR 1.79, 95% CI 0.94–3.39).[25] Several investigators reported higher incidences of adverse events in elderly patients with locally advanced NSCLC, even though they had a similar survival benefit.[26–28] Furthermore, better clinical outcomes were reported in elderly patients (>70 years) by thoracic radiotherapy rather than chemoradiotherapy with a similar regimen for younger patients.[29,30] Based on these reports, it is necessary to develop an optimal treatment strategy, especially to find the best chemotherapy regimen combined with thoracic radiotherapy, for elderly patients with stage III NSCLC.

This study had several limitations. First, the proportion of patients with stage IIIA disease was relatively high compared to previous phase III trials, which might have a favorable effect on overall survival.[13,14] Second, the population included in this analysis was relatively younger than those reported by Segawa *et al.*[13] and had better prognosis than real world patients. As discussed in this article, younger age might be a better prognostic factor in concurrent chemoradiotherapy (Table 3). The third limitation is potential selection bias in a highly selected population suitable for early phase clinical trials. To enable to follow clinical and prognostic information with the least missing data, however, we selected the patients that participated in the current phase I and feasibility trial of docetaxel consolidation.

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In conclusion, approximately 15% of patients with unresectable stage III NSCLC could be cured with chemoradiotherapy without severe late toxicities after 10 months of follow-up. Although based on the data from a highly selected population participated in phase I and phase II trial, this analysis would strengthen and confirm the previous reports concerning concurrent chemoradiotherapy with third generation cytotoxic agents.

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Preliminary analysis of risk factors for late rectal toxicity after helical tomotherapy for prostate cancer

Natsuo TOMITA[1,*], Norihito SOGA[2], Yuji OGURA[2], Norio HAYASHI[2], Hidetoshi SHIMIZU[1], Takashi KUBOTA[1], Junji ITO[1], Kimiko HIRATA[1], Yukihiko OHSHIMA[1], Hiroyuki TACHIBANA[1] and Takeshi KODAIRA[1]

[1]Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusaku, Nagoya 464-8681, Japan
[2]Department of Urology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusaku, Nagoya 464-8681, Japan
*Corresponding author. Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusaku, Nagoya 464-8681, Japan. Tel: +81-52-762-6111; Fax: +81-52-752-8390; Email: ntomita@aichi-cc.jp

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The purpose of this study is to examine risk factors for late rectal toxicity for localized prostate cancer patients treated with helical tomotherapy (HT). The patient cohort of this retrospective study was composed of 241 patients treated with HT and followed up regularly. Toxicity levels were scored according to the Radiation Therapy Oncology Group grading scale. The clinical and dosimetric potential factors increasing the risk of late rectal toxicity, such as age, diabetes, anticoagulants, prior abdominal surgery, prescribed dose, maximum dose of the rectum, and the percentage of the rectum covered by 70 Gy (V70), 60 Gy (V60), 40 Gy (V40) and 20 Gy (V20) were compared between ≤ Grade 1 and ≥ Grade 2 toxicity groups using the Student's t-test. Multivariable logistic regression analysis of the factors that appeared to be associated with the risk of late rectal toxicity (as determined by the Student's t-test) was performed. The median follow-up time was 35 months. Late Grade 2–3 rectal toxicity was observed in 18 patients (7.4%). Age, the maximum dose of the rectum, V70 and V60 of the ≥ Grade 2 toxicity group were significantly higher than in those of the ≤ Grade 1 toxicity group ($P = 0.00093$, 0.048, 0.0030 and 0.0021, respectively). No factor was significant in the multivariable analysis. The result of this study indicates that the risk of late rectal toxicity correlates with the rectal volume exposed to high doses of HT for localized prostate cancer. Further follow-up and data accumulation may establish dose–volume modeling to predict rectal complications after HT.

Keywords: prostate cancer; helical tomotherapy; late toxicity; intensity-modulated radiation therapy; image-guided radiation therapy

INTRODUCTION

Intensity-modulated radiation therapy (IMRT) has been shown to reduce late rectal toxicity in high-dose external beam radiation therapy (EBRT) for prostate cancer [1], but essential issues remain to be solved. Factors increasing the risk of late rectal toxicity include not only the prescribed dose and radiation technique delivering the dose, but also some clinical characteristics. Major factors reportedly associated with rectal complication risks include diabetes mellitus [1, 2], advanced age [3], androgen deprivation therapy (ADT) [4], rectum size [5], and prior abdominal surgery [6]. In addition, acute rectal toxicity is now recognized to be associated with an increased risk of developing late rectal complications [7]. Rectum volumes at especially high-dose areas on the dose–volume histogram (DVH) also have an impact on late rectal toxicity. The following dose–volume constraints are provided as a conservative starting point for 3-dimensional conformal radiotherapy (3DCRT): V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 < 15% [8], which have been derived from some 3DCRT experiences. However, such conventional dose–volume constraints may not be valuable in current clinical practices because the significance of IMRT has already been established in EBRT for localized prostate cancer [9]. IMRT planning yields DVH curves in distinctly different

shapes from those of forward-planned 3DCRT. In fact, the ratio of IMRT vs 3DCRT increased from 0.15% in the year 2000 to 95.9% in the year 2008 in the United States [10]. The significance of image-guided radiation therapy (IGRT) has also been established in this category [9]. Thus, dose–volume modeling derived from non-image guided 3DCRT may inevitably be modified to predict complications derived from image-guided IMRT (IG-IMRT). Data are, however, still too poor or insufficient to address dose–volume constraints in this modern combination technique.

Helical tomotherapy (HT, TomoTherapy, Madison, WI) is a form of IMRT, and detectors within the tomotherapy system provide megavolt–age computed tomographic (MVCT) images of patients, which can be obtained immediately before processes for setup, registration, and repositioning (i.e. IGRT). Next, we examined the impact of patient clinical characteristics and DVH parameters on late rectal toxicity after HT treatment for non-metastatic prostate cancer. We report the results of the examinations. It is of particular interest to describe dose–volume modeling to predict rectal complications after HT.

MATERIALS AND METHODS

Patients and treatment methods

A total of 241 consecutive patients clinically diagnosed with non-metastatic prostate cancer, who were treated with HT between June 2006 and December 2010 and followed up regularly at our institution, were enrolled in this study. Written informed consent for the treatment and an anonymous data application were obtained from each of the patients before the treatment. Pretreatment evaluations, androgen deprivation therapy (ADT), and HT treatment were described circumstantially in our previous study [11]. In brief, the clinical target volume (CTV) was defined as the entire prostate and the proximal seminal vesicle. The planning target volume 1 (PTV1) included the CTV with a 6–8 mm margin except for the prostatorectal interface, where a 4–6 mm margin was used. Outside PTV1, PTV2 was defined as the seminal vesicle with a similar margin to that of PTV1. By our definition, only the rectum around the PTV1 area with a cranio-caudal 10-mm margin is delineated as an organ at risk. Prescribed doses were PTV1 D95 (i.e. dose delivered to 95% of PTV1): 74 Gy in the low-risk group, 78 Gy in the intermediate- and high-risk groups, and PTV2 D95: 64 Gy in all of the risk groups. Patients had a tube inserted or were encouraged to defecate when their rectums were dilated on daily MVCT, and were checked on MVCT again.

Follow-up evaluations and data collection

Follow-up evaluations after the treatment were performed at 3-month intervals. Toxicity levels were scored according to the Radiation Therapy Oncology Group (RTOG) morbidity grading scale [12]. In brief, Grade 1 toxicity represents minimal side effects not requiring medication for symptom control; Grade 2 toxicity indicates symptoms requiring medication; Grade 3 indicates complications requiring minor surgical intervention (i.e. laser coagulation); and Grade 4 requires hospitalization and major intervention. The time until the occurrence of late toxicity was represented as the period from the start date of HT.

Patient characteristics (e.g. age, T-stage, diabetes mellitus, anticoagulants, and history of abdominal surgery) and DVH parameters (prescribed dose, PTV volume, rectal volume, mean dose of the rectum, maximum dose of the rectum, the percentage of the rectum at least covered by 70 Gy [V70], 60 Gy [V60], 40 Gy [V40], or 20 Gy [V20]) were collected from the patients on their initial visits to our departments. Total ADT time and acute and late rectal toxicities were reviewed on the patients' charts in the analysis. The prescribed dose on the DVH and the practically delivered dose varied from one another in seven of the patients, because of HT cessation for a range of reasons such as acute rectal symptoms. Practically delivered doses were 74 Gy in six of the patients and 70 Gy in one patient, despite the prescribed dose of 78 Gy on the DVH. In these patients, the prescribed dose, the mean dose of the rectum, the maximum dose of the rectum, V70, V60, V40, and V20 were approximately shown by these values on the DVH × practically delivered dose (70 or 74 Gy)/prescribed dose on the DVH (78 Gy) in this analysis. Table 1 shows patient characteristics and DVH parameters for this patient cohort.

Statistical analyses

The impact of clinical and dosimetric factors on Grade 2 or higher late rectal toxicity was analyzed. The clinical and dosimetric potential factors increasing the risk of late rectal toxicity were compared between the ≤ Grade 1 and the ≥ Grade 2 toxicity groups and were then analyzed by the Student's t-test. The following factors were examined: the patient characteristics described above, total ADT time, the presence of Grade 2 or higher acute rectal toxicity, and the DVH parameters described above. Multivariable logistic regression analysis was carried out for the factors that previously appeared to be associated with the risk of late rectal toxicity by the Student's t-test ($P < 0.10$). Significance was determined at a P value of <0.05.

RESULTS

Late rectal toxicity

The median follow-up time from the start of HT was 35 months (range, 13–66 months). Rectal toxicity has been described in detail in our previous study [11]. Briefly, 18 (7.4%) of the patients developed late Grade 2 or 3 rectal toxicity. Of the 16 patients (6.6%) who developed late

Table 1. Patient characteristics and DVH parameters

Characteristic	Total	($n = 241$)
Age (years)	69	(49–81)
PSA level (ng/ml)	15.17	(1.40–502.00)
Gleason score	7	(5–10)
Tumor stage		
T1–T2	109	(45.2%)
T3–T4	132	(54.8%)
Risk group		
Low	17	(7.0%)
Intermediate	53	(22.0%)
High	171	(71.0%)
Diabetes (%)	23	(9.5%)
Anticoagulants (%)	41	(17.0%)
Abdominal surgery (%)	21	(9.4%)
ADT (month)	27	(4–92)
≥ Grade 2 acute toxicity (%)	27	(11.2%)
PTV volume (cc)	59.0	(20.7–190.9)
Rectum volume (cc)	41.9	(21.8–113.7)
Prescribed dose (Gy)	78.0	(70.0–78.0)
Rectum mean dose (Gy)	38.8	(27.0–46.4)
Rectum max dose (Gy)	80.2	(70.1–83.8)
V70 (%)	7.2	(0.1–13.6)
V60 (%)	15.5	(1.9–25.6)
V40 (%)	38.1	(20.0–77.8)
V20 (%)	90.0	(45.0–100.0)

DVH = dose-volume histogram, ADT = androgen deprivation therapy, V dose = the percentage of the rectum at least covered by each dose; PTV = planning target volume. Age, PSA, ADT and DVH parameters are represented as mean and ranges.

Grade 2 rectal toxicity, 13 developed Grade 2 rectal bleeding. Other Grade 2 symptoms were pain on defecation in two of the patients and subtle fecal incontinence in one of the patients. Two patients (0.8%) developed Grade 3 rectal bleeding requiring laser coagulation. No Grade 4 late rectal complications were observed. Figure 1 shows the rate of developing late Grade 2 or higher rectal toxicity in the time course after HT.

Analysis of risk factors associated with late rectal toxicity

Table 2 shows the effects of patient characteristics and DVH parameters on Grade 2 or higher late rectal toxicity as analyzed by the Student's t-test. Age, maximum dose of the rectum, V70, and V60 were significantly variable between the ≤ Grade 1 and the ≥ Grade 2 toxicity groups as analyzed by the Student's t-test ($P = 0.00093$, 0.048, 0.0030 and 0.0021, respectively). To further evaluate the independent effects of the factors that displayed a P-value <0.10 by the Student's t-test, such as age, anticoagulants, the maximum dose of the rectum, V70 and V60 on ≥ Grade 2 late rectal toxicity, a multivariable logistic regression analysis was performed. None of the factors were found to be significantly correlated by this analysis, as shown in Table 3.

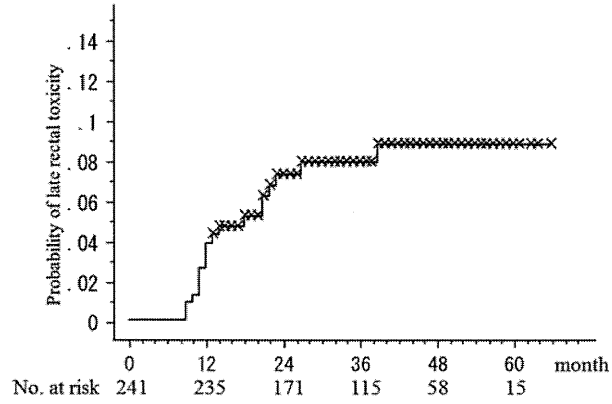

Fig. 1. The rate of developing late ≥ Grade 2 rectal toxicity after helical tomotherapy.

Figure 2 shows the mean DVH and standard deviations (SD) of patients with or without Grade 2 or higher late rectal toxicity after HT. The maximum dose of the rectum, V70, V60, V40 and V20 for patients with ≥ Grade 2 late rectal toxicity vs those with ≤ Grade 1 late rectal toxicity were 80.1 ± 2.0 Gy vs 79.2 ± 3.3 Gy, 9.0 ± 2.9% vs 6.8 ± 3.5%, 17.6 ± 3.5% vs 14.8 ± 5.0%, 39.6 ± 8.4% vs 39.9 ± 8.7%, and 84.7 ± 10.3% vs 87.1 ± 10.1%, respectively.

DISCUSSION

The DVH curves of IMRT are distinctly different from those of forward-planned 3DCRT. The combined use of IGRT may also have a possible impact on the DVH difference between IGRT and non-IGRT treatments because significant margin reduction between the prostate and PTV could be implemented clinically with the combined use of IGRT [13]. The results of the present study indicate that the risk of late rectal toxicity correlates with the rectal volume exposed to high doses in the HT treatment (i.e. IG-IMRT) for localized prostate cancer, although there were no significant factors in the multivariable logistic regression analysis. This suggestion is consistent with other reports derived from the 3DCRT data. Kuban *et al.* assessed the impact of 70 Gy vs 78 Gy doses on gastro-intestinal (GI) toxicity in 301 patients treated with 3DCRT. After a median follow-up

Table 2. The effects of patient characteristics and DVH parameters on ≥ Grade 2 late rectal toxicity after helical tomotherapy, as analyzed by the Student's t-test

Characteristic	≤ Grade 1 ($n = 223$)	≥ Grade 2 ($n = 18$)	*P*-value
Age (years)	68.5 ± 6.1	71.2 ± 4.2	0.0093*
Tumor stage (≥T3)	55.2%	50.0%	0.34
Diabetes (%)	9.4%	11.1%	0.42
Anticoagulants (%)	15.7%	33.3%	0.074
Abdominal surgery (%)	9.0%	5.6%	0.28
ADT (≥27 months)	48.4%	27.8%	0.26
Acute toxicity (%)	11.7%	5.6%	0.11
PTV volume (cc)	62.1 ± 22.9	66.6 ± 18.3	0.17
Rectum volume (cc)	44.5 ± 13.9	42.1 ± 16.4	0.28
Prescribed dose (Gy)	77.5 ± 1.4	77.3 ± 1.5	0.28
Rectum mean dose (Gy)	39.2 ± 5.0	38.6 ± 3.5	0.27
Rectum max dose (Gy)	79.2 ± 3.3	80.1 ± 2.0	0.048*
V70 (%)	6.8 ± 3.5	9.0 ± 2.9	0.0030*
V60 (%)	14.8 ± 5.0	17.6 ± 3.5	0.0021*
V40 (%)	39.9 ± 8.7	39.5 ± 8.4	0.43
V20 (%)	87.1 ± 10.1	84.7 ± 10.3	0.18

DVH = dose-volume histogram, ADT = androgen deprivation therapy, V dose = the percentage of the rectum at least covered by each dose. Age and DVH parameters are represented as mean ± SD. *Statistically significant.

Table 3. The effects of patient characteristics and DVH parameters on ≥ Grade 2 late rectal toxicity after helical tomotherapy, as analyzed by multivariable logistic regression analysis

Characteristic	*P*-value	Hazard ratio (CI)
Age (years)	0.10	1.08 (0.99–1.19)
Anticoagulants (%)	0.12	2.18 (0.81–5.88)
Rectum max dose (Gy)	0.87	0.99 (0.82–1.19)
V70 (%)	0.16	1.30 (0.91–1.85)
V60 (%)	0.85	0.98 (0.78–1.23)

DVH = dose–volume histogram, ADT = androgen deprivation therapy, V dose = the percentage of the rectum at least covered by each dose, CI = 95% confidence interval, NA = not applicable.

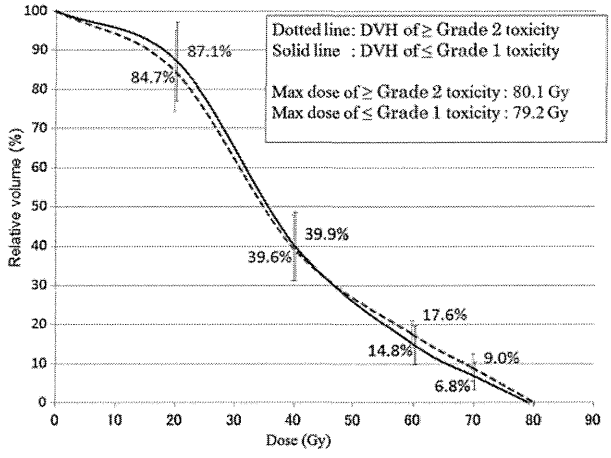

Fig. 2. The mean dose–volume histograms and standard deviations (SD) of patients with or without ≥ Grade 2 late rectal toxicity after helical tomotherapy.

period of 8.7 years, GI toxicity more severe than RTOG Grade 2 was often observed in high-dose patients (28% vs 15%; $P = 0.013$). DVH analysis showed that the incidence of complications could be significantly decreased by reducing the volume of the treated rectum. When <25% of the rectum was treated with >70 Gy, the Grade 2-or-greater complication incidence at 6 years post-treatment was much reduced, 16% as compared with 46% when this dose–volume cutoff point was exceeded [14]. Tucker *et al.* also analyzed DVH data from 1009 patients treated with 3DCRT on RTOG protocol 94-06. In these data, no evidence was found of any influence of the intermediate doses on the risk of ≥ Grade 2 late rectal toxicities. The critical dose for this endpoint seemed to be ≥75 Gy [15]. The results of our present study suggests that patients with advanced age are at risk of rectal complication. The routine

medication of anticoagulants may be also associated with rectal bleeding, as shown in Table 2 and 3. These results are in line with the reports of Skwarchuk *et al.* [3] and Pederson *et al.* [16]. Even when optimal dose–volume constraints are applied, rectal complications can still occur due to clinical factors such as anticoagulant medications or advanced age.

Most of the mature published clinical data on dose-related rectal toxicity originate from 3DCRT. Some data derived from 3DCRT experiences recommended V60 < 35% and V70 < 20% as a conservative starting point for the dose–volume constraints for 3DCRT [8]. As shown in Table 1, the mean values of V70 and V60 were 7.2 (range, 0.1–13.6) and 15.5 (range, 1.9–25.6), respectively, in this patient cohort treated with HT. Although these values fulfill the terms of the conventional dose–volume constraints described above, we observed late Grade 2 or 3 rectal toxicities in 7.4% of the patients. This result indicates that tighter dose–volume constraints of the rectum would be necessary for IG-IMRT than the conventional constraints derived from the clinical data of 3DCRT. On the other hand, caution should be taken in interpreting this result, because Fig. 2 simply shows the mean DVH with or without Grade 2 or higher late rectal toxicity. In fact, the SDs of patients with or without late rectal toxicity overlapped considerably at each of the doses, as shown in Fig. 2. Further follow-up and data accumulation are needed to evaluate the clinical significance of the small absolute difference in the high-dose areas. To our knowledge, only one study has investigated dosimetric risk factors for late rectal toxicity after IMRT. Pederson *et al.* have reported that the incidence of ≥ Grade 2 rectal toxicity was 5% in 296 consecutive patients treated with IMRT with a median follow-up period of 41 months [16]. They found that 100% of men with rectal V70 ≤ 10%, V65 ≤ 20%, and V40 ≤ 40% were free from ≥ Grade 2 rectal toxicity; 92% of men with rectal V70 ≤ 20%, V65 ≤ 40%, and V40 ≤ 80% as well as 85% of men exceeding these criteria were also free from the toxicity. The results of their study together with those of our study also suggest that more stringent dose–volume constraints are necessary for IMRT compared with 3DCRT.

The reliability of this study resides in the use of IGRT involving MVCT. The position of the rectum at the time of the treatment planning CT scan is likely not fully representative of the position during RT because of intrafraction variations in rectal filling, intestinal gas, and bladder filling. We think that these uncertainties have little influence on the present study because we checked these situations carefully in both the CT simulation and the pretreatment MVCT, and because patients had a tube inserted or were encouraged to defecate as necessary. On the other hand, two essential points need to be considered when interpreting the results of this study. Firstly, we need to define the rectum. This study has specified rectal lengths only around the PTV1 area with a cranio-caudal 10-mm margin. However, DVH studies so far have used variable definitions for the rectum [8, 16]. The rectosigmoid flexure is an uncertainty as the superior limit in determining where the rectum starts. The inferior limit has been variably defined as being at the level of the anal verge, the ischial tuberosities, or above the anus. Our definition of the rectum has been reasonably accepted so far among physicians. It is frequently contoured as a solid, and we have adopted this definition in our study. Secondly, we need to consider the problem of the diversity of the toxicity. We brought together all late rectal symptoms in the analyses of factors associated with late rectal toxicity, including some types of sequelae such as rectal bleeding, pain on defecation, and fecal incontinence. Refined knowledge of the location of dose maximums in combination with separate scoring and modeling of the different aspects of rectal toxicity clarifies specific anatomic regions of dose sensitivity [8]. However, the symptoms were mostly rectal bleeding in this study (15 of 18 patients who developed late Grade 2 or 3 rectal toxicity). We considered that lumping all rectal symptoms had little influence on the results of this study.

The treatment of rectal bleeding is also a critical issue in high-dose EBRT for prostate cancer. Takemoto *et al.* evaluated the results of the treatment for hemorrhagic proctitis after IMRT for prostate cancer [17]. Among 403 patients treated with IMRT, 64 developed late rectal bleeding with a median follow-up time of 35 months. Most patients were ameliorated with the steroid suppositories as medication, or even without any treatment, but one patient treated with steroid enemas for 12 months developed septic shock and died of multiple organ failure. All of the 12 patients treated with Argon plasma coagulation (APC) were ameliorated in that study. They concluded that steroid suppositories/enemas and APC were effective, although a short duration of the administration with an appropriate steroid dosage is recommended. We also treated patients developing rectal bleeding with steroid suppositories. Two of these patients showed no response to steroid suppositories so they then received APC. All patients with Grade 2 or 3 rectal bleeding got an improvement with steroid suppositories or APC in our present study, as in the report by Takemoto *et al.*

In conclusion, we have demonstrated the impact of patient clinical characteristics and DVH parameters on late rectal toxicity in a large number of non-metastatic prostate cancer patients after HT treatment. Late Grade 2–3 rectal toxicities were observed in 7.4% of the patients. The result of this study indicates that the risk of late rectal toxicity correlates with increase in age and the rectal volume exposed to high doses in HT treatment for localized prostate cancer. Further follow-up and data accumulation may establish dose–volume modeling to predict rectal complications after HT.

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